

Hyperbaric oxygen therapy mitigates cochlear damage induced by a high-fructose diet: a histopathological study in rats

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ABSTRACT

Aims: Hearing loss, an increasing worldwide issue, has been associated with increased carbohydrate consumption. This study investigates the histopathological impact of a high-fructose diet (HFD) on cochlear structures and assesses whether hyperbaric oxygen therapy (HBOT) can mitigate those effects.

Methods: Adult male Wistar rats were divided into four groups (n=8 each): control (standard diet, 10 weeks), HFD (60% fructose diet, 10 weeks), HBOT (standard diet+daily HBOT at 2.4 ATA for 1 h during weeks 9–10), and HFD+HBOT (60% fructose diet+HBOT in weeks 9–10). After 10 weeks, cochleae were taken out and stria vascularis thickness, basilar membrane thickness, and inner/outer hair cell lengths were measured in basal, middle, and apical turns. Cochlear cross-sections stained with H&E and Masson's trichrome, and evaluated histopathologically under light microscope.

Results: Compared to controls, HFD-fed rats had thinner stria vascularis and basilar membranes in basal and intermediate turns and shorter hair cell lengths throughout all turns. The apical turn outer hair cell length and the middle and apical turns inner hair cell length increased statistically in HFD+HBOT rats compared to HFD alone. No significant changes were seen between HBOT-only and control groups. HFD induces considerable cochlear damage and cellular death in the organ of Corti in subjects. HBOT application somewhat mitigates these effects.

Conclusion: A 10-week HFD induces region-specific cochlear structural degeneration in rats, and HBOT during the final two weeks partially reverses these changes. Future studies with larger sample sizes should include functional auditory assessments and explore underlying molecular mechanisms.

Keywords: Hyperbaric oxygen therapy, high-fructose diet, inner hair cell, organ of Corti, outer hair cell

INTRODUCTION

Hearing loss represents a significant global health challenge, with substantial implications for individual well-being, educational achievement, and economic productivity. According to the World Health Organization, approximately 430 million people worldwide currently experience disabling hearing loss, and this number is projected to rise to 700 million by 2050.¹ The etiology of hearing loss is multifactorial, involving both genetic predispositions and environmental exposures—such as chronic noise exposure, the use of ototoxic medications, and nutritional status.²

Among environmental contributors, dietary factors have emerged as important modifiable risks. In a five-year prospective cohort study of 2,448 adults aged 50 and older, participants in the highest quintile of dietary glycemic load faced a 76% greater risk of developing age-related hearing loss compared with those consuming a low-glycemic-load diet.³ Moreover, poor long-term glycemic control, reflected

by an HbA1c level of 6.3% or higher, has been independently associated with increased odds of hearing impairment.⁴

Over the past several decades, fructose consumption has increased substantially, driven largely by the widespread intake of sugar-sweetened beverages and processed foods.^{5,6} The high-fructose diet (HFD) has been extensively examined and is consistently linked to increased oxidative stress and systemic inflammation.⁷⁻⁹ In cochlear hair cells, elevated reactive oxygen species (ROS) can indiscriminately damage lipids, proteins, and nucleic acids, leading to cytochrome C release and subsequent caspase-3-mediated apoptosis.¹⁰ Moreover, the combination of inflammatory signaling and oxidative stress can activate programmed cell-death pathways—such as ferroptosis and necroptosis—culminating in irreversible loss of cochlear hair cells.¹¹ HFD has also been shown to impair nitric oxide (NO) production, contributing to endothelial dysfunction and various cardiovascular disorders.^{12,13} In the cochlea, basal NO synthesis is critical

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for maintaining proper blood flow.¹⁴ Despite these well-documented metabolic and vascular effects, the direct impact of an HFD on cochlear function and overall hearing remains largely unknown.

Hyperbaric oxygen therapy (HBOT) has been investigated for treating different types of hearing loss, especially sudden sensorineural hearing loss (SSNHL) and noise-induced hearing loss (NIHL).¹⁵ Clinical studies indicate that HBOT combined with corticosteroids significantly improves hearing recovery in SSNHL patients.¹⁶⁻¹⁸ Similarly, in NIHL, HBOT plus corticosteroids yields better outcomes than HBOT alone.¹⁹⁻²¹

We hypothesize that HFD causes cochlear damage and HBOT can counteract this effect, preserving cochlear tissue integrity. To test this, we will evaluate HBOT’s therapeutic potential by assessing histopathological and histomorphometric changes in cochlear tissue after fructose exposure.

METHODS

Ethics

All procedures involving animals were approved by the Animal Experiments Local Ethics Committee of Erciyes University (ERU HADYEK) (Date: 08.01.2025, Decision No: 25/025). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Animals and Diet

Thirty-two adult male Wistar rats (10 weeks old, 250–300 g) were housed under standard laboratory conditions (22±2°C; 12-hour light/dark cycle) with ad libitum access to water and food. High fructose diet (60 kcal% fructose; Cat. No. ARD-60kcal.F; Arden Feed Industry, Ankara, Türkiye) was used in the HFD and HFD+HBOT groups.

Experimental Design

Rats were randomly divided into four groups (n=8 per group) as indicated below. The Control group received a standard rodent diet throughout the study. The HFD group was fed the HFD for the full 10 weeks. The HBOT group received the standard diet for 10 weeks, with the addition of daily hyperbaric oxygen treatments (100 % O₂ at 2.4 ATA for 1 hour) during the final two weeks (weeks 9– 10). Finally, the HFD+HBOT group was fed the HFD for 10 weeks and, during weeks 9– 10, underwent the same daily hyperbaric oxygen regimen (2.4 ATA for 1 hour). At the end of week 10, all animals were euthanized by decapitation, and their cochlear tissues were harvested for histopathological and histomorphometric analysis (Table 1).

Histopathological Examination

For histological examination, the cochlear tissues from the rats were fixed in a 10% formaldehyde solution for 72 h. After fixation, the tissues underwent decalcification in a solution prepared with 10% formaldehyde+80% distilled water and 10% nitric acid. Following decalcification, routine histological tissue processing procedures were applied. Briefly, tissues were washed in running tap water, passed through increasing concentrations of alcohol, cleared with xylene, embedded in paraffin blocks. Twenty- two serial sections, each 5 µm in

Table 1. General design of the study										
Groups (n=8)	Weeks									
	1	2	3	4	5	6	7	8	9	10
Control group	Standard rodent diet									
The high-fructose (HFD) diet group	High-fructose diet									
Hyperbaric oxygen (HBOT) group	Standard rodent diet									
	Daily hyperbaric oxygen treatment (100% O ₂ at 2.4 ATA for 1 hour)									
HFD+HBOT group	High-fructose diet									

thickness, were prepared from these blocks and subsequently mounted on glass slides. Sections were stained with Masson’s Trichrome (MT) to assess connective tissue structure and with Hematoxylin Eosin (H&E) to examine the overall histologic structure. Histopathological evaluation was conducted using an Olympus BX51 light microscope (Olympus Corp., Tokyo, Japan). The thickness of the stria vascularis and basilar membrane, as well as the lengths of outer and inner hair cells, were measured using ImageJ software, and the results underwent statistical analysis.

Statistical Analysis

All data analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows version 22.0. Comparisons between control and experimental groups were conducted using One-Way Analysis of Variance (ANOVA) for normally distributed variables, with multiple comparisons performed using the Tukey test where differences were observed. Results were presented as mean±standard deviation, with p values less than 0.05 deemed statistically significant.

RESULTS

Histopathological Analysis

Upon evaluation of the images from all groups using light microscopy, it was noted that the cochlea maintained its cylindrical morphology, and the organ of Corti was readily identifiable in the basal, medial, and apical regions of the cochlea, which completed 2.5 rotations around the modiolus, situated along the vertical axis at the center. Upon evaluation of the light microscopic pictures from the control and HBOT groups, it was noted that the scala media was delineated from the scala tympani by the basilar membrane and from the scala vestibule by the Reissner membrane. The architecture of the stria vascularis, including intermediate, marginal, and basal cells, together with many blood vessels, was readily identifiable in light microscopic pictures and extended to the Reissner membrane. The tectorial membrane, a gelatinous structure composed of parallel collagen fibers, sprang from the spiral lamina and enveloped the organ of Corti (Figure). Furthermore, it was noted that the organ of Corti, located on the basilar membrane that divides the scala tympani and scala media, functions as a specialized auditory receptor and had a consistent structure in both groups. Upon examination of the center of Corti using a light microscope at 40x magnification, it was seen that the outside hair cells were organized in three

rows, while the inner hair cells were grouped in a single row, exhibiting sensory receptor characteristics. Deiter cells, situated at the base of hair cells, supported them by their cytoplasmic extensions and were characterized by nuclei positioned on the basilar membrane. The pillar cells, situated centrally inside the organ of Corti and exhibiting a triangular morphology, were discerned on each side of the Corti tunnel by the positioning of their nuclei at the vertices of the triangle. Following the outer hair cells, arranged in three rows, the Hensen, Böttcher, and Claudius cells, which performed a supportive role, had a systematic configuration (**Figure**). It was concluded that excessive fructose consumption adversely impacted all components of the inner ear, with the most significant damage occurring in the basal turn of the cochlea. Cytoplasmic and nuclear condensation, together with distortion of the basilar membrane, marginal cell loss, and vacuolization in the stria vascularis of the lateral portion of the scala media were seen. Ruptures were identified in the Reissner membrane situated between the scala vestibuli and the scala media, and structural anomalies were seen in the tectorial membrane, where the gelatinous matrix and collagen fibers were aligned in parallel. The most notable discovery was the occurrence of cellular losses accompanied by hydropic and vacuolar degeneration in the organ of Corti. The cells exhibited enlarged cytoplasm, reduced nuclei, and expanded intercellular gaps (**Figure**). In contrast to the HFD group, the organ of Corti in the HFD+HBOT group demonstrated a more regular structure, with reduced spacing between the marginal cells of the stria vascularis, and the Reissner membrane, situated between the scala media and scala vestibuli, maintained its integrity (**Figure**). The cytoplasmic and nuclear condensation seen in the basilar membrane of the HFD group was reduced in the HFD+HBOT group. The tectorial membrane, characterized by a gelatinous composition of parallel collagen fibers, had a more organized structure than the HFD group, however less so than the control group. Simultaneously, in the HFD+HBOT group, the loss of supporting cells, as well as outer and inner hair cells constituting the organ of Corti, was less pronounced than in the HFD group. Furthermore, the intercellular gaps inside the organ of Corti diminished, and the nuclei became more pronounced. Furthermore, the tunnel of Corti and the

adjacent pillar cells had a more organized structure relative to the HFD group (**Figure**).

The histological evaluation measured the thickness of the stria vascularis, the lengths of outer and inner hair cells, and the thickness of the basilar membrane in the basal, middle, and apical turns of the cochlea. In the basal and middle turns, stria vascularis thickness was significantly reduced in the HFD group compared to both the control and HBOT groups. Although the HFD+HBOT group showed increased stria vascularis thickness relative to the HFD group, this increase did not reach statistical significance. In the apical turn, stria vascularis thickness was comparable among all groups (**Table 2**).

Outer hair cell length in the basal and middle turns was significantly shorter in the HFD group than in the Control and HBOT groups. In the HFD+HBOT group, outer hair cell length in these turns was higher than in the HFD group, but again, the difference was not statistically significant. In the apical turn, HFD reduced outer hair cell length compared to Control and HBOT, whereas HFD+HBOT produced a significant increase in outer hair cell length compared to HFD (**Table 2**).

Inner hair cell length was significantly decreased in the HFD group in the apical and middle turns relative to control and HBOT. The HFD+HBOT group exhibited significantly greater inner hair cell length in these turns compared to HFD. In the basal turn, inner hair cell length was significantly lower in HFD versus Control and HBOT, and although HFD+HBOT showed an increase versus HFD, this change was not statistically significant (**Table 2**).

For the basilar membrane, thickness in the basal and middle turns was significantly reduced in HFD compared to Control and HBOT. The HFD+HBOT group demonstrated an increase in basilar membrane thickness relative to HFD, but without statistical significance. No significant differences were observed in basilar membrane thickness among groups in the apical turn (**Table 2**).

DISCUSSION

This study shows that a 10-week HFD leads to notable structural damage in the basal and middle turns of the stria vascularis and basilar membrane, along with the apical, middle, and basal turns of cochlear hair cells. HBOT partially

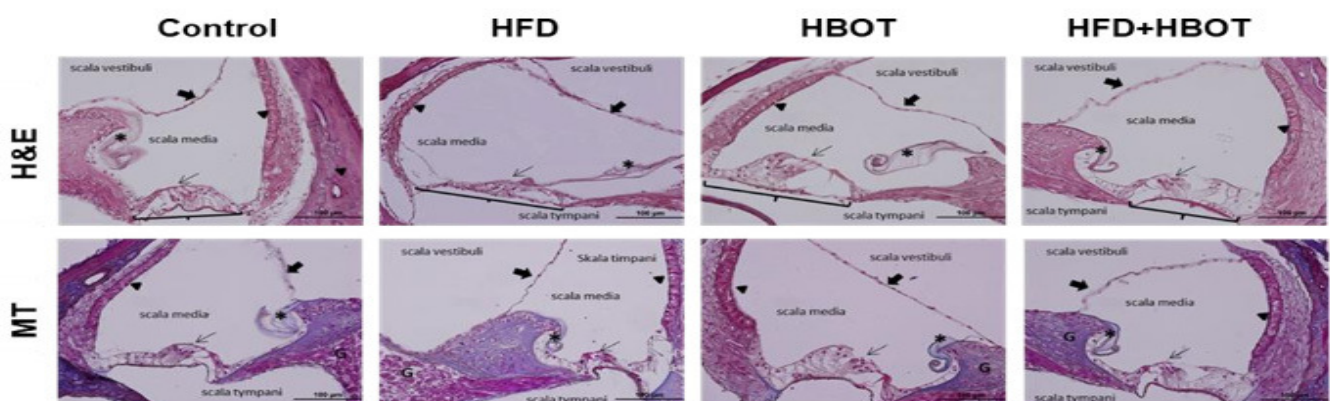


Figure. Images of groups with H&E and MT stainings. Representative cochlear cross-sections stained with H&E (top row) and Masson's trichrome (MT, bottom row) in control, high-fat diet (HFD), hyperbaric oxygen therapy (HBOT), and HFD+HBOT groups (scale bar=100 μ m). Arrowhead (▶) indicates the stria vascularis; thick arrow (→) indicates Reissner's membrane; asterisk (*) indicates the tectorial membrane; thin arrow (→) indicates outer hair cells; and G indicates the spiral ganglion

Table 2. Statistical results of differences in basal, medial, and apical regions between the control and experimental groups

		Control	HFD	HBOT	HFD+HBOT	p
Stria vascularis	Apical	23.17±2.23	21.37±1.08	22.62±1.38	22.16±0.99	.072
	Middle	18.82±0.86 ^a	16.24±0.94 ^b	19.28±0.68 ^a	17.04±0.68 ^b	.001
	Basal	14.23±1.07 ^a	12.20±1.13 ^b	14.98±0.65 ^a	13.03±0.88 ^b	.001
Outer hair cell length	Apical	36.94±4.88 ^a	22.66±2.69 ^b	34.12±3.59 ^{ac}	31.62±3.42 ^c	.001
	Middle	24.59±3.77 ^a	19.12±1.30 ^b	24.75±2.68 ^a	20.95±2.96 ^b	.001
	Basal	20.66±6.17 ^a	15.28±3.92 ^b	19.81±2.09 ^{ab}	16.91±3.05 ^{ab}	.020
Inner hair cell length	Apical	42.89±3.57 ^a	35.09±1.83 ^b	41.90±3.68 ^{ac}	38.53±1.62 ^c	.001
	Middle	32.88±1.42 ^a	28.00±1.27 ^b	31.84±1.31 ^a	29.88±1.24 ^c	.001
	Basal	24.56±4.10 ^a	20.31±2.53 ^b	23.88±2.88 ^a	21.57±1.54 ^{ab}	.008
Basilar membrane	Apical	4.71±0.44	4.39±0.45	4.76±0.84	4.50±0.34	.410
	Middle	5.92±0.46 ^a	5.25±0.50 ^b	6.00±0.43 ^a	5.53±0.34 ^{ab}	.002
	Basal	8.38±1.45 ^a	7.03±0.50 ^b	8.11±1.17 ^a	7.73±0.98 ^{ab}	.050

Histomorphometric measurements (μm) of cochlear structures in control, high-fructose diet (HFD), hyperbaric oxygen therapy (HBOT), and HFD+HBOT groups. Values are presented as mean±SD (n=8 per group). Different superscript letters (a–c) within the same row indicate statistically significant differences between groups (p<0.05). SD: Standard deviation

alleviated these effects, resulting in significant increases in hair cell length in the apical cochlear region and indicating trends toward recovery in other substructures. This study is the first to establish a direct connection between HFD and cochlear damage, while also identifying HBOT as a potential treatment for diet-related auditory impairments.

The structural changes observed in HFD-exposed cochleae are consistent with established mechanisms by which fructose elevates oxidative stress, promotes systemic inflammation, and induces vascular damage.^{7-9,12} Furthermore, epidemiological data show that high-glycemic-load diets are linked to hearing loss. For example, Gopinath et al.³ found that adults in the highest glycemic load quintile had a 76% higher risk of age-related hearing loss. In stria vascularis, Shi et al.²³ reported that increased oxidative stress was linked to reduced cell density, mitochondrial membrane potential collapse, and release of cytochrome c and AIF, triggering pericyte apoptosis. loss of these pericytes compromised the blood-labyrinth barrier as shown by Evans blue leakage in diabetic cochleae and led to stria vascularis cell loss and vessel dropout. Similarly, in cochlear hair cells, elevated ROS caused cytochrome c release and caspase-3-mediated apoptosis,¹⁰ and inflammatory signaling combined with oxidative stress activated programmed cell-death pathways such as ferroptosis and necroptosis, resulting in irreversible hair cell loss.¹¹ Basilar membrane thinning in HFD groups mirrors findings by Guo et al.,²⁴ who showed that D-galactose-induced oxidative stress led to mitochondrial dysfunction and apoptosis in basilar membrane cells, mimicking age-related cochlear degeneration. The relative preservation of the apical turn's stria vascularis and basilar membrane thickness can be attributed to lower susceptibility to vascular changes. For instance, research has shown significant loss of vessel density in the basal turn in conditions like presbycusis, while the apical turn remains relatively preserved.²⁵

HBOT's demonstrated benefits in treating both SSNHL and NIHL offer a valuable framework for interpreting its protective effects in this study. Because the cochlea relies on

a single terminal artery (the labyrinthine artery) and has a high oxygen demand, it is particularly susceptible to hypoxic injury.²⁶ By substantially increasing the partial pressure of oxygen in the perilymph, HBOT minimizes ischemic damage in SSNHL, which may similarly counteract the vascular impairment induced by HFD.^{12,26} Furthermore, HBOT upregulates constitutive nitric oxide synthase (NOS) in the cochlea, helping to preserve cochlear blood flow and potentially offsetting HFD-related reductions in NO production.^{13,27} Although HBOT elevates tissue oxygen levels, it paradoxically lowers oxidative stress by boosting antioxidant enzyme activity, thereby protecting cochlear cells from HFD-induced oxidative damage.²⁸ In addition, HBOT promotes angiogenesis and stimulates the release of growth factors such as insulin-like growth factor 1 (IGF-1), which may facilitate repair of injured cochlear cells.²⁹ Finally, its anti-inflammatory actions in SSNHL correlate with improved auditory outcomes, suggesting that HBOT could also mitigate the inflammatory response triggered by an HFD.³⁰

These results underscore that high fructose intake may pose significant risks to auditory function, indicating that dietary modifications could be essential for preserving hearing. The observation that HBOT provides partial protection points to its promise as a treatment for diet-induced cochlear injury. Nevertheless, translating these findings into clinical practice will require additional human studies to establish optimal treatment protocols and identify which patients are most likely to benefit.

Limitations

There are some limitations to our study, which can be listed as follows: 1. A HFD can lead to clinical conditions such as prediabetes, insulin resistance, and obesity. Initial and final weight gain changes, Blood glucose, HbA1C, insulin, blood lipids, and liver enzymes were not measured in the study. We emphasize that these should be measured in future studies and that correlations with histological data should be investigated. 2. Only male rats were used, due to reasons such as time, budget, and animal availability. As authors, we must point out that the

use of female subjects is important from a translational medicine perspective and in terms of reflecting public health.

CONCLUSION

This study illustrates that a HFD induces considerable cochlear damage and cellular death in the organ of Corti in subjects. HBOT somewhat mitigates these effects, notably enhancing outer hair cell longevity in the apical turn and promoting inner hair cell proliferation in both the apical and middle turns. The findings indicate that elevated fructose consumption may present considerable hazards to processing functions and propose HBOT as a potential therapeutic intervention. More extensive investigations are required to assess alternative and mechanical hearing results and to potentially facilitate the clinical adoption of HBOT regimens.

ETHICAL DECLARATIONS

Ethics Committee Approval

All procedures involving animals were approved by the Animal Experiments Local Ethics Committee of Erciyes University (ERU HADYEK) (Date: 08.01.2025, Decision No: 25/025).

Informed Consent

As it is an animal study, free and informed consent is not required.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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